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Retinal Microvascular signs and 10-Year Risk of Cerebral Atrophy: The ARIC Study

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Abstract

Background and purpose—Cerebral atrophy, detected as ventricular enlargement (VE) or sulcal widening (SW) on magnetic resonance imaging (MRI), is recognized as a risk factor for vascular dementia or Alzheimer's disease. However, its underlying pathophysiology is not known. We examined whether retinal microvascular assessment could provide predictive information on the risk of VE and SW on MRI.

Methods—A prospective, population-based study of 810 middle-aged persons without clinical stroke or MRI infarcts. All participants had a first cranial MRI and retinal photography in 1993-95, and returned for a repeated MRI in 2004-06 (median follow-up of 10.5 years). Retinal photographs were graded for presence of retinopathy and retinal microvascular abnormalities, and MRI images were graded for ventricular size (VS) and sulcal size (SS) according to standardized protocols. VE

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and SW were defined as an increase in VS or SS of ≥3 of 10 grades between baseline and follow-up.

Results—After adjusting for age, gender and cardiovascular risk factors, retinopathy and arterio-venous nicking at baseline were associated with 10-year VE (odds ratio [OR] and 95% confidence interval [CI]: 2.03, 1.20-4.42 for retinopathy and 2.19, 1.23-3.90 for arterio-venous nicking). Retinal signs were not associated with 10-year SW.

Conclusions—Retinopathy and arteriovenous nicking are predictive of long-term risk of VE, but not of SW, independent of cardiovascular risk factors. These data support a microvascular etiology for subcortical but not cortical cerebral atrophy.

Keywords

Cerebral atrophy; Ventricular enlargement; Sulcal widening; Retinal microvascular signs

Cerebral atrophy, detected on magnetic resonance imaging (MRI) as ventricular enlargement (VE) or sulcal widening (SW),1 has been shown to be associated with cognitive impairment. 2 Semi-quantitative assessment of ventricular size based on MRI is recognized as a risk marker for dementia3 and Alzheimer's disease (AD)4, and it accelerates during the pre-AD stage of amnestic mild cognitive impairment5, thus providing complementary information for diagnosis and monitoring of neurodegenerative diseases.4, 6 While neurodegenerative processes clearly play an essential role in the pathophysiology of cerebral atrophy,[7] reduced cerebral perfusion due to microvascular disease may also contribute to the development of cerebral atrophy.[8]

The retina provides a non-invasive window to study microvascular etiology of cerebrovascular disease.[9] Pathologic retinal changes may reflect micro-angiopathic processes in the brain. In the Atherosclerosis Risk in Communities (ARIC) study, we have previously demonstrated cross-sectional associations between retinal signs and VE and SW.[10] and both cross-sectional and longitudinal associations with cognitive decline10, 11 In this study, we examine the prospective relationship of retinal microvascular abnormalities to the 10- year incidence of VE and SW in the ARIC cohort.

METHODS

Study Population

The ARIC Study is a population-based study of cardiovascular disease among 15,792 middle-aged African American and whites from 4 United States communities.10 Participants who underwent a third examination in 1993-95 for cerebral MRI and retinal photography, when participants were 51 to 72 years of age, were included for this study.10 Cerebral MRI was performed for persons aged ≥55 years in two ARIC centers.[12] Of the 1,684 participants who had completed cerebral MRI and retinal examinations at the third visit, 1,031 (61%) had a repeated MRI examination in 2004-06 (median follow-up of 10.5 years). Of these, 810 participants were included after excluding those with a history of clinical/MRI-defined stroke or incomplete examinations. Although there were no significant differences in gender, race/ethnicity, or lipid profile, included participants were younger and had less hypertension, diabetes, and smoking, and less carotid intima-media thickness. Institutional review boards at each study site approved the study and informed consent was obtained from all participants.

T1-,T2-, and proton density- weighted axial cerebral MRI scans oriented parallel to the anterior commissure–posterior commissure line were obtained.[10] Masked neuroradiologists evaluated the digitized MRI scan. SS and VS were assessed on a semi-quantitative 10-point scale by

visual comparison with standard images. Incident VE and SW were defined as an increase in VS and SS grade of ≥3 between baseline and follow-up.

Retinal photographs were taken through a non-pharmacologically dilated pupil.[10, 13] Trained graders evaluated the photographs using a standardized protocol.[10] Retinopathy was defined as present if any of the following lesions were detected: retinal microaneurysms, hemorrhages, soft exudates, and other less common lesions. Retinal arterio-venous nicking and focal arteriolar narrowing was separately defined as present if graded definite or probable. Retinal vessel diameters were measured using standardized semi-automated imaging software.[13]

Participants underwent standardized examinations.[10] Mean arterial blood pressure (MABP) was computed as 2/3 x [diastolic blood pressure] + 1/3 x [systolic blood pressure]. Diabetes mellitus was defined as fasting/non-fasting glucose level of ≥126mg/dL/ ≥200mg/dL, or a self-report of physician-diagnosed diabetes or treatment for diabetes.

Statistical Analysis

We constructed multiple logistic regression models to determine odds ratios (OR) for 10-year cumulative incidence of VE or SW in relation to retinal microvascular signs, adjusting for age, gender, race/ethnicity and study center, and further adjusted for cigarette smoking, 6-year average of MABP between 1987-89 and 1993-95, anti-hypertensive medication, education, fasting glucose, total cholesterol, triglycerides and carotid intima-media thickness (IMT).

RESULTS

Over a median follow-up of 10.5years, 147 (18.4%) had 10-year incident VE, and 94 (11.8%) had 10-year incident of SW. Table 1 shows that retinopathy and arterio-venous nicking were associated with increased odds of 10-year VE (OR 2.03 and OR 2.19, respectively) after adjusting for cardiovascular risk factors. Although not significant, cotton wool spots (OR 2.57) and hard exudates (OR 2.43) seemed to have stronger associations with 10-year incident VE. No retinal signs were associated with 10-year incident SW. There were no significant associations of retinal arteriolar or venular diameter with 10-year incident VE or SW (data not shown).

DISCUSSION

In this prospective population-based study, persons with retinal microvascular signs had a two-fold risk of incident VE over a 10-year period. This finding expands our previous cross-sectional observation,[10] and suggests that microvascular disease may be a risk factor for VE.

In contrast, we found no associations between retinal microvascular signs and incident SW. It is consistent with previous studies reporting that VE had a stronger association with a test for verbal learning and recent memory compared to SW.[14, 15] This could reflect closer correlation of retinal microvascular changes with cerebral vessels in deeper parts of the brain responsible for VE than those affecting the sulci, suggesting that microvascular disease, as expected,[11] plays a more prominent role in the development of sub-cortical than cortical atrophy. Alternatively, the lack of association of retinal signs with SW could be due to measurement error, because SS was less reliably measured (kappa-value for agreement of VS and SS were 0.89 and 0.66, respectively).[1, 8]

In regard to the potential vascular contribution to AD, the pathogenesis of AD principally involves neurodegeneration, but for any level of neurodegeneration, the added effects of ischemia and infarction could be additive, and reduce the threshold at which clinical symptoms occur. Alternatively, it is possible that microvascular disease alters the disposition of beta-

amyloid and leads to higher levels of brain beta-amyloid, thereby facilitating the appearance of clinical symptoms. In our study, cotton wool spots (a sign of acute micro-infarction) and hard exudates (a sign of disruption in retinal microvasculature from hypoxia) were most strongly associated with VE, consistent with a microvascular contribution to AD.

The strengths of this study include its prospective design, biracial cohort of African Americans and whites, and standardized assessment. Limitations may include possible selection bias because of significant lost to follow-up and confounding effect of un-measured risk factors.

SUMMARY

Our study showed that retinal microvascular signs are associated with the 10-year incident cerebral atrophy reflected as VE. This finding suggests that retinal microvascular signs may represent risk factors for subcortical atrophy evident before radiological manifestations or cognitive decline. Our finding also suggests a contribution of microvascular etiology of cerebral atrophy in addition to neurodegenerative pathologies, and supports the concept that modification of microvascular disease risk factors (e.g., hypertension, diabetes) may reduced progression of cerebral atrophy.

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Table 1

Retinal Microvascular Changes and Ventricular Enlargement or Sulcal Widening (≥3 grade increase in ventricular size or sulcal size, respectively)

Retinal microvascular abnormalities		Ventricular Enlargement, N=147 (18.4%)			Sulcal Widening, N=94 (11.8%)		
		No. at Risk (% VE)	Age-gender-race-study center adjusted OR (95% CI)	Multivariable* OR (95% CI)	*No. at Risk (% SW)*	Age-gender-race-study center adjusted OR (95% CI)	Multivariable* OR (95% CI)
Any retinopathy	Absent	*748 (17.8)*	1.00	1.00	*748 (11.8)*	1.00	1.00
	Present	*53 (27.5)*	1.76 (0.92, 3.40)	2.03 (1.02, 4.42)	*53 (11.8)*	1.09 (0.45, 2.66)	1.03 (0.37, 2.90)
Microaneurysm	Absent	*689 (17.7)*	1.00	1.00	*689 (11.8)*	1.00	1.00
	Present	*26 (23.1)*	1.34 (0.52, 3.46)	1.84 (0.60, 5.63)	*26 (15.4)*	1.56 (0.51, 4.76)	2.09 (0.58, 7.47)
Retinal hemorrhage	Absent	*739 (17.9)*	1.00	1.00	*739 (11.6)*	1.00	1.00
	Present	*22 (27.3)*	1.77 (0.67, 4.68)	1.47 (0.47, 4.61)	*22 (13.6)*	1.45 (0.41, 5.11)	1.89 (0.48, 7.40)
Cotton wool spot	Absent	*766 (17.9)*	1.00	1.00	*766 (11.9)*	1.00	1.00
	Present	*13 (38.5)*	3.06 (0.97, 9.71)	2.57 (0.67, 9.85)	*13 (23.1)*	2.43 (0.64, 9.27)	1.85 (0.34, 10.07)
Hard Exudates	Absent	*743 (17.9)*	1.00	1.00	*743 (11.8)*	1.00	1.00
	Present	*10 (30.0)*	2.17 (0.54, 8.68)	2.43 (0.46, 12.87)	*10 (20.0)*	2.39 (0.48, 11.86)	5.02 (0.69, 36.35)
Arterio-venous nicking	Absent	*685 (17.4)*	1.00	1.00	*685 (11.5)*	1.00	1.00
	Present	*98 (27.6)*	1.78 (1.08, 2.92)	2.19 (1.23, 3.90)	*98 (12.2)*	1.05 (0.54, 2.02)	1.37 (0.67, 2.81)
Focal arteriolar narrowing	Absent	*654 (18.5)*	1.00	1.00	*654 (11.2)*	1.00	1.00
	Present	*110 (18.2)*	0.94 (0.55, 1.59)	1.13 (0.61, 2.10)	*110 (13.6)*	1.10 (0.60, 2.01)	1.30 (0.66, 2.55)

OR: Odds ratio, 95%CI: 95% confidence interval.

*Further adjusted for cigarette smoking, 6-year mean arteriolar blood pressure, anti-hypertensive medication, education, fasting glucose, total cholesterol, triglycerides and carotid intima-media thickness.